

Disclosed are
ABSTRACT

KK 11/10/01

Therapies for the treatment of a variety of central nervous system injuries including acute or chronic spinal cord injury, traumatic brain injury, and white matter stroke involve the administration of rho protein inhibitors to promote axon regeneration. Local administration is employed in typical embodiments, and 5 this may include injection of a recombinant virus that expresses an inhibitor. In one embodiment, the inhibitor is *C. botulinum* C3 exoenzyme or a chimeric *C. botulinum* C2/C3 construct expressed in a replication-deficient adeno, adeno-associated, or herpes virus.



PCT

Exhibit "A"

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|--|--|---|--|
| <p>(51) International Patent Classification ⁶ : A01N 63/00, C12N 15/64, 5/00, A61K 38/00, A01N 43/04</p> | | A1 | <p>(11) International Publication Number: WO 99/08533</p> <p>(43) International Publication Date: 25 February 1999 (25.02.99)</p> |
| <p>(21) International Application Number: PCT/US98/16794</p> | | <p>(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> | |
| <p>(22) International Filing Date: 12 August 1998 (12.08.98)</p> | | | |
| <p>(30) Priority Data: 60/055,268 13 August 1997 (13.08.97) US</p> | | <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> | |
| <p>(71) Applicant (for all designated States except US): YALE UNIVERSITY [US/US]; Office of Cooperative Research, 155 Whitney Avenue, New Haven, CT 06520-8336 (US).</p> | | | |
| <p>(72) Inventor; and</p> | | | |
| <p>(75) Inventor/Applicant (for US only): STRITTMATTER, Stephen, M. [US/US]; 26 Pleasant Valley Road, Clinton, CT 06413 (US).</p> | | | |
| <p>(74) Agent: KRINSKY, Mary, M.; 88 Prospect Street, New Haven, CT 06511-3797 (US).</p> | | | |

(54) Title: CENTRAL NERVOUS SYSTEM AXON REGENERATION

(57) Abstract

Therapies for the treatment of a variety of central nervous system injuries including acute or chronic spinal cord injury, traumatic brain injury, and white matter stroke involve the administration of rho protein inhibitors to promote axon regeneration. Local administration is employed in typical embodiments, and this may include injection of a recombinant virus that expresses an inhibitor. In one embodiment, the inhibitor is *C. botulinum* C3 exoenzyme or a chimeric *C. botulinum* C2/C3 construct expressed in a replication-deficient adeno-adenovirus, or herpes virus.